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Brief communication

Cardiorespiratory fitness and future risk of pneumonia: a long-term prospective cohort study

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Abstract

Purpose: We aimed to assess the prospective association of cardiorespiratory fitness (CRF) with the risk of pneumonia.

Methods: Cardiorespiratory fitness, as measured by maximal oxygen uptake (VO_{2max}), was assessed using a respiratory gas exchange analyser in 2,244 middle-aged men in the Kuopio Ischemic Heart Disease cohort. We corrected for within-person variability in CRF levels using data from repeat measurements taken several years apart.

Results: During a median follow-up of 25.8 years, 369 men received a hospital diagnosis of pneumonia.

The age-adjusted regression dilution ratio of CRF was 0.58 (95% confidence interval: 0.53-0.63).

Cardiorespiratory fitness was linearly associated with pneumonia risk. The hazard ratio (95% confidence interval) for pneumonia per 1 standard deviation increase in CRF in analysis adjusted for several risk factors for pneumonia was 0.77 (0.68-0.87). The association remained consistent on additional adjustment for total energy intake, socioeconomic status, physical activity, and C-reactive protein 0.82 (0.72-0.94). The corresponding adjusted hazard ratios (95% confidence intervals) were 0.58 (0.41-0.80) and 0.67 (0.48-0.95) respectively, when comparing the extreme quartiles of CRF levels.

Conclusions: Our findings indicate a graded inverse and independent association between CRF and the future risk of pneumonia in a general male population.

Keywords: cardiorespiratory fitness; maximal oxygen uptake; pneumonia; cohort study

List of abbreviations

Chronic obstructive pulmonary disease (COPD)

Cardiorespiratory fitness (CRF)

Confidence interval (CI)

Hazard ratio (HR)

Kuopio Ischaemic Heart Disease (KIHD)

Maximal oxygen uptake ($\text{VO}_{2\text{max}}$)

Standard deviation (SD)

Introduction

Pneumonia, which is an inflammatory condition of the lung tissue usually caused by infection with viruses or bacteria, affects about 450 million people worldwide and causes approximately 4 million deaths annually.[1] It is a leading cause of mortality among the elderly, the young, and people with comorbid conditions.[1] Even with the advent of new antimicrobial strategies in the last several decades, mortality from pneumonia continues to increase.[2] Pneumonia is also associated with substantial morbidity and high economic costs. The annual global economic cost of community-acquired pneumonia has been estimated at \$17 billion.[2] Major risk factors which predispose to pneumonia include smoking, excessive alcohol consumption, respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD), and other chronic conditions such as kidney and liver disease.[2] Pneumonia constitutes a substantial public health burden and is a preventable health condition. Regular physical activity is well known to have important health benefits, and which include long-term protection against adverse vascular and non-vascular outcomes[3, 4]. Physical activity has also been shown to improve acute and long-term prognosis of pneumonia in elderly patients.[5] Cardiorespiratory fitness (CRF), as measured by maximal oxygen uptake (VO_{2max}), is the gold standard for assessing aerobic capacity and is an index of the level of physical activity.[6] Cardiorespiratory fitness has also been consistently shown to be independently and inversely associated with vascular and non-vascular outcomes.[7] Taken the overall evidence, we postulated that CRF may be linked to the risk of pneumonia. In this context, we aimed to assess the prospective association of CRF with risk of pneumonia, using a study which comprised a population-based cohort of 2244 Caucasian men.

Materials and methods

Our analyses employed the Kuopio Ischemic Heart Disease risk factor study which comprised a general population-based sample of middle-aged men aged 42-61 years who were recruited from Kuopio in eastern Finland. Baseline examinations were conducted between March 1984 and December 1989. There

was a total of 3433 randomly selected men who were potentially eligible and of these, 3235 were eligible for inclusion into the study. Of the 3235 men, 553 declined to give informed consent or did not respond to the invitation and 2682 volunteered to participate in the study. There were 314 men who were unable to undergo exercise testing because of orthopaedic and musculoskeletal issues, leaving 2368 men with complete information on CRF. Less than 1% of data was missing for covariates considered in the analysis with no missing data for the outcome, which left 2244 men with complete information on CRF, covariates, and cases for the current analysis. All study procedures were conducted according to the Declaration of Helsinki and the Research Ethics Committee of the University of Eastern Finland approved the study protocol. Recruitment methods and assessment of risk markers have been described in previous reports.[8] Cardiorespiratory fitness was measured using maximal oxygen uptake, which was estimated using a respiratory gas exchange analyzer during cycle ergometer exercise tests. A detailed description of the measurement of VO_{2max} has been reported previously.[8] We also performed repeat measurements of VO_{2max} 10 years apart in a random subset of participants. All incident cases of pneumonia that occurred from study entry to 2014 were included; these were collected by linkage to the National Hospital Discharge Register and comprehensive review of hospital records. The diagnoses of pneumonia cases were made by qualified physicians based on the International Classification of Diseases codes used in clinical practice. We calculated hazard ratios (HRs) with 95% confidence intervals (CIs) using Cox proportional hazard models. All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

Results

The mean [standard deviation (SD)] age and CRF of study subjects at study entry were 53 (5) years and 30.3 (8.0) ml/kg/min respectively. During a median (interquartile range) follow-up of 25.8 (17.4-27.9) years, a total of 369 hospital diagnosed pneumonia cases occurred (annual rate 7.46/1000 person-years at risk; 95% CI 6.74 to 8.26). The overall age-adjusted regression dilution ratio of CRF was 0.58 (95% CI:

0.53 to 0.63), implying that using baseline measurements of CRF could underestimate the association between CRF and pneumonia risk by $[(1/0.58)-1]*100 = 72\%$. On adjustment for several risk factors (age, smoking status, history of diabetes, prevalent history of coronary heart disease, history of asthma, history of chronic bronchitis, history of tuberculosis, years of education, and alcohol consumption), CRF was inversely associated with risk of pneumonia in a graded dose-response fashion (**Figure**). The HR for pneumonia per 1 SD increase in CRF in analysis adjusted for age was 0.67 (95% CI: 0.60 to 0.76), which was slightly attenuated on further adjustment for several risk factors for pneumonia 0.77 (95% CI: 0.68 to 0.87). The association remained consistent on additional adjustment for total energy intake, socioeconomic status, physical activity, and C-reactive protein 0.82 (95% CI: 0.72 to 0.94). The corresponding adjusted HRs were 0.42 (95% CI: 0.31 to 0.58), 0.58 (95% CI: 0.41 to 0.80), and 0.67 (95% CI: 0.48 to 0.95) respectively, when comparing the extreme quartiles of CRF levels. The associations were stronger after correction for within-person variability in CRF levels (**Table**).

Discussion

The present investigation is the first study to examine the prospective association between CRF and risk of pneumonia in a general population-based cohort of middle-aged Caucasian men. Our results demonstrate an inverse dose-response relationship between CRF and future risk of pneumonia. The association was independent of several well established risk factors such as age, smoking, alcohol consumption, history of diabetes, and other comorbidities. Pneumonia is an inflammatory condition of the lung tissue[9], which suggests that CRF may influence its pathogenesis via the anti-inflammatory effects of regular physical activity combined with good cardio-respiratory function among most fit individuals.[10] Physical activity has been shown to decrease the risk of mortality as well as several chronic diseases.[3, 4] Mechanisms proposed include beneficial modulation in levels of cardiovascular risk markers, haemostatic factors, adipokines, and sex hormones.[11] We postulate that these mechanisms may underpin the protective association observed between CRF and pneumonia risk. Direct effects of

physical activity on target organs and tissues have also been implicated;[12] the increasing demand of ventilation during progressive physical exercise may mechanically improve and increase the amount of ventilation in pulmonary airways, bronchioles and alveoli. We however call for further research to (i) delineate the mechanistic pathways explaining the observed association between optimal CRF and lower pneumonia risk, (ii) replicate these findings, and (iii) evaluate if additional information on CRF levels can be used identify individuals at high risk of pneumonia.

Strengths of the current study include the population-based prospective cohort design, the large sample size, representativeness of the sample in the general population, the long and complete follow-up of all participants with prospectively collected outcome events data, detailed information on several relevant covariates, and the comprehensive analysis which included assessment of the dose-response relationship between CRF and risk of pneumonia, as well as correction for within-person variability in CRF levels. Our study also has limitations which should be considered. This relatively homogenous population consisted of predominantly white males and therefore the results cannot yet be generalised to women or other populations. The possibility of residual confounding cannot be eliminated due to measurement errors in some covariates or unmeasured relevant confounders such as influenza immunisation status, lung function, and other health modifying behaviours. There may also be biases due to lack of data on specific types of pneumonia and the possibility of exclusion of undiagnosed pneumonia or cases that were not treated at a health facility (e.g., treated at home).

In conclusion, CRF is strongly and independently associated with reduced risk of pneumonia in middle-aged Caucasian men, which was consistent with a graded dose-response relationship. Further research is needed to evaluate if CRF will have prognostic significance for long-term risk of pneumonia in the general population or in some specific patient populations.

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Author Contributions

S.K.K. researched data, analyzed data and wrote the manuscript. S.K.K., T.L. and J.A.L. contributed to data collection, reviewed and edited the manuscript. S.K.K. is the guarantor and had full access to all the data in the study and takes responsibility for the integrity of the data and the decision to submit and publish the manuscript.

Disclosures

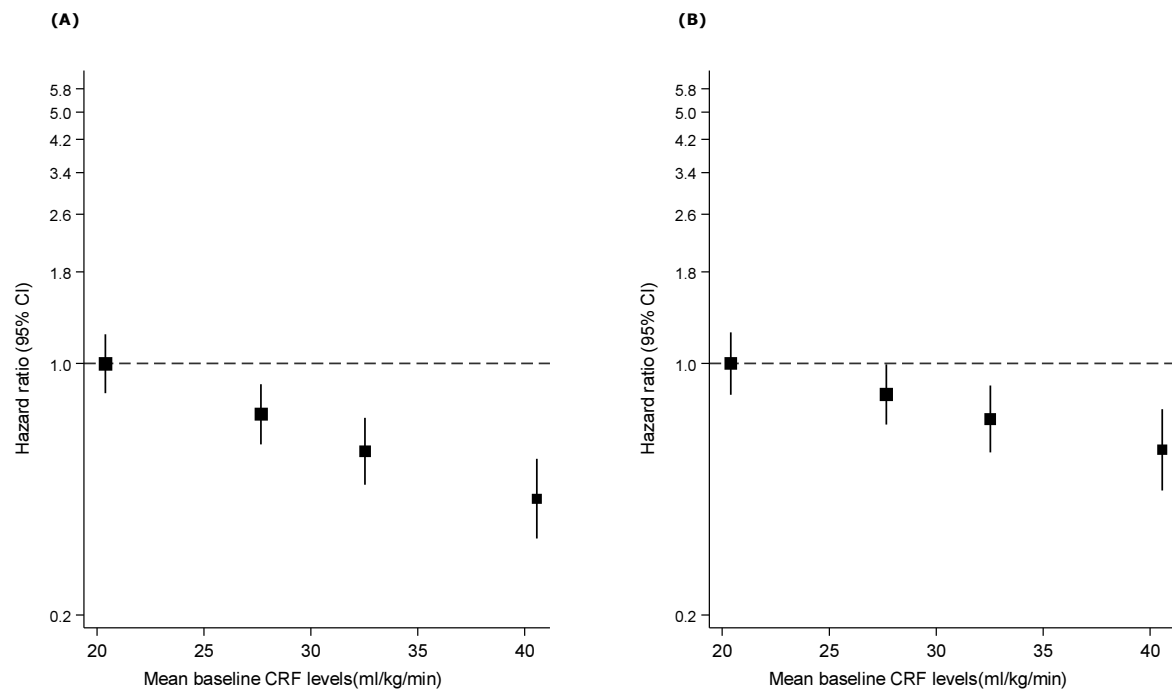
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Figure legend

Figure. Hazard ratios for pneumonia, by quartiles of baseline levels of cardiorespiratory fitness



A, adjusted for age; **B**, adjusted for age, smoking status, history of diabetes, prevalent coronary heart disease, history of asthma, history of chronic bronchitis, history of tuberculosis, years of education, total cholesterol, and alcohol consumption
CRF, cardiorespiratory fitness

Table. Association between cardiorespiratory fitness and risk of pneumonia

CRF (ml/kg/min)	Events/ Total	Model 1		Model 2		Model 3	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Baseline CRF							
Per 1 SD increase	369 / 2,244	0.67 (0.60 to 0.76)	< 0.001	0.77 (0.68 to 0.87)	< 0.001	0.82 (0.72 to 0.94)	0.003
Q1 (6.36-25.15)	120 / 561	ref		ref		ref	
Q2 (25.16-30.03)	103 / 561	0.72 (0.56 to 0.94)	0.017	0.82 (0.63 to 1.08)	0.151	0.88 (0.67 to 1.15)	0.340
Q3 (30.04-35.16)	84 / 561	0.57 (0.43 to 0.76)	< 0.001	0.70 (0.52 to 0.94)	0.018	0.78 (0.58 to 1.06)	0.110
Q4 (35.16-65.40)	62 / 561	0.42 (0.31 to 0.58)	< 0.001	0.58 (0.41 to 0.80)	0.001	0.67 (0.48 to 0.95)	0.023
Usual CRF*							
Per 1 SD increase	369 / 2,244	0.50 (0.41 to 0.62)	< 0.001	0.64 (0.51 to 0.79)	< 0.001	0.71 (0.57 to 0.89)	0.003
Q1 (6.36-25.15)	120 / 561	ref		ref		ref	
Q2 (25.16-30.03)	103 / 561	0.57 (0.36 to 0.90)	0.017	0.71 (0.45 to 1.13)	0.151	0.80 (0.50 to 1.27)	0.340
Q3 (30.04-35.16)	84 / 561	0.38 (0.23 to 0.62)	< 0.001	0.54 (0.33 to 0.90)	0.018	0.66 (0.39 to 1.10)	0.110
Q4 (35.16-65.40)	62 / 561	0.23 (0.13 to 0.39)	< 0.001	0.39 (0.22 to 0.68)	0.001	0.51 (0.28 to 0.91)	0.023

CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio; ref, reference; Q, quartile; SD, standard deviation;

*, indicates correction for within-person variability in values of CRF, that is, the extent to which an individual's CRF measurements vary around a long-term average value ("usual CRF values")

Model 1: Adjusted for age

Model 2: Model 1 plus smoking status, history of diabetes, prevalent coronary heart disease, history of asthma, history of chronic bronchitis, history of tuberculosis, years of education, total cholesterol, and alcohol consumption

Model 3: Model 2 plus total energy intake, socioeconomic status, physical activity, and C-reactive protein